CLAIMS

WE CLAIM:

1. A method for making a humanized antibody comprising amino acid sequence of a non-human, import antibody and a human antibody, comprising the steps of:

   a. obtaining the amino acid sequences of at least a portion of an import variable domain and of a consensus human variable domain;

   b. identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human amino variable domain sequences;

   c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;

   d. aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;

   e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;

   f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:

      1. non-covalently binds antigen directly,

      2. interacts with a CDR; or

      3. participates in the V_L - V_H interface; and

   g. for any non-homologous import antibody amino acid residue which is reasonably expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence.

2. The method of claim 1, having an additional step of determining if

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any such non-homologous residues are exposed on the surface of the domain or buried within it, and if the residue is exposed, retaining the consensus residue.

3. The method of claim 1, having the additional steps of searching the import variable domain sequence for glycosylation sites, determining if any such glycosylation site is reasonably expected to affect the antigen binding or affinity of the antibody, and if so, substituting the glycosylation site into the consensus sequence.

4. The method of claim 1, having the additional steps of searching the consensus variable domain sequence for glycosylation sites which are not present at the corresponding amino acid in the import sequence, and if the glycosylation site is not present in the import sequence, substituting the import amino acid residues for the amino acid residues comprising the consensus glycosylation site.

5. The method of claim 1, having an additional step which comprises aligning import antibody and consensus antibody FR sequences, identifying import antibody FR residues which are non-homologous with the aligned consensus FR sequence, and for each such non-homologous import antibody FR residue, determining if the corresponding consensus antibody residue represents a residue which is highly conserved across all species at that site, and if it is so conserved, preparing a humanized antibody which comprises the consensus antibody amino acid residue at that site.

6. The method of claim 1, wherein the corresponding consensus antibody residues are selected from the group consisting of 4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 68H, 69H, 70H, 73H, 74H, 75H,

76H, 78H, 91H, 92H, 93H, and 103H.

7. A method comprising providing at least a portion of an import, non-human antibody variable domain amino acid sequence having a CDR and a FR, obtaining the amino acid sequence of at least a portion of a consensus human antibody variable domain having a CDR and a FR, substituting the non-human CDR for the human CDR in the consensus human antibody variable domain, and then substituting an amino acid residue for the consensus amino acid residue at at least one of the following sites:
4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.

8. The method of claim 7, wherein the substituted residue is the residue found at the corresponding location of the non-human antibody.

9. A humanized antibody variable domain having a non-human CDR incorporated into a human antibody variable domain, wherein the improvement comprises substituting an amino acid residue for the human residue at a site selected from the group consisting of:
4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.

10. The humanized antibody variable domain of claim 9, wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR was obtained.

11. The humanized antibody variable domain of claim 9, wherein no human FR residue other than those set forth in the group has been substituted.

12. A polypeptide comprising the amino acid sequence:
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLESGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHY
TTPPTFGQGTKVEIKRT

13. A polypeptide comprising the sequence:
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLE
WVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDT
AVYYCSRWGGDGFYAMDVWGQGTLVTVSS

14. A computer comprising the sequence data of the following amino acid sequence:
   a. DIQMTQSPSSLSASVGDRVTITCRASQDVSSYLAWYQQ
   KPGKAPKLLIYAASSLESGVPSRFSGSGSGTDFTLTISSLQ
   PEDFATYYCQQYNSLPYTFGQGTKVEIKRT, or
   b. EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVR
   QAPGKGLEWVAVISENGGYTRYADSVKGRFTISADTSKN
   TAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDVWGQG
   TLVTVSS

15. A computer representation of the following amino acid sequence:
   a. DIQMTQSPSSLSASVGDRVTITCRASQDVSSYLAWYQQ
   KPGKAPKLLIYAASSLESGVPSRFSGSGSGTDFTLTISSLQ
   PEDFATYYCQQYNSLPYTFGQGTKVEIKRT, or
   b. EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVR
   QAPGKGLEWVAVISENGGYTRYADSVKGRFTISADTSKN
   TAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDVWGQG

TLVTVSS

16. A method comprising storing a computer representation of the following amino acid sequence:

a. DIQMTQSPSSLSASVGDRVTITCRASQDVSSYLAWYQQ KPGKAPKLLIYAASSLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQYNSLPYTFGQGTKVEIKRT, or

b. EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVR QAPGKGLEWVAVISENGGYTRYADSVKGRFTISADTSKN TAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDVWGQG TLVTVSS